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Case Report: Successful Drug Desensitization to Ustekinumab in an Adult Patient with Crohn's Disease

Vaka Raporu: Crohn Hastalığı Olan Yetişkin Bir Hastada Ustekinumab'a Karşı Başarılı İlaç Desensitizasyonu

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ABSTRACT

Ustekinumab is a biological agent used in the treatment of inflammatory diseases. Since biological therapies are targeted therapies, their use is increasing, and the incidence of related reactions is increasing accordingly. We present this case because we successfully desensitized a patient who experienced a ustekinumab reaction. An adult Crohn's disease patient who experienced an adverse reaction to the fifth subcutaneous dose of Ustekinumab was evaluated in our Immunology and Allergy clinic. The patient was successfully treated using the stepwise rapid drug desensitization protocol. We present this case to emphasize the importance and awareness of desensitization in managing drug reactions in clinics such as Dermatology, Rheumatology, and Gastroenterology, where the drug is widely used.

Keywords: Bbiological therapy, Crohn's Disease, desensitization, Ustekinumab.

ÖZET

Ustekinumab, inflamatuar hastalıkların tedavisinde kullanılan biyolojik bir ajandır. Biyolojik tedaviler hedefli tedaviler olduğundan, kullanımları artmakta ve buna bağlı olarak ilgili reaksiyonların görülme sıklığı artmaktadır. Bu olguyu, ustekinumab reaksiyonu yaşayan bir hastayı başarıyla duyarsızlaştırdığımız için sunuyoruz. Ustekinumab'ın beşinci subkutan dozuna karşı olumsuz reaksiyon yaşayan yetişkin bir Crohn Hastalığı hastası, İmmünoloji ve Alerji kliniğimizde değerlendirildi. Hasta, kademeli hızlı ilaç duyarsızlaştırma protokolü kullanılarak başarıyla tedavi edildi. Bu olguyu, ilacın yaygın olarak kullanıldığı Dermatoloji, Romatoloji ve Gastroenteroloji gibi kliniklerde ilaç reaksiyonlarının yönetiminde duyarsızlaştırmanın önemini ve farkındalığını vurgulamak için sunuyoruz.

Anahtar Sözcükler: Biyolojik tedavi, Crohn Hastalığı, duyarsızlaştırma, Ustekinumab.

Introduction

Ustekinumab is a fully human monoclonal antibody that targets the p40 subunit shared by interleukin (IL)-12 and IL-23 (1). It is approved for the treatment of psoriasis, psoriatic arthritis, and inflammatory bowel disease. In 2016, both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved Ustekinumab for adults (≥18 years) with moderately to severely active Crohn's disease who have failed or are intolerant to immunomodulators, corticosteroids, and tumor necrosis factor (TNF) antagonists (2,3). Biological therapies are increasingly used to treat oncologic, immunologic, and inflammatory conditions as targeted therapies (4). Psoriasis is believed to result from a dysregulated type 1 immune response, characterized by elevated cytokines such as IL-12 and IL-23. These cytokines activate IL-17-producing T cells, which play a role in inflammation leading to joint damage in psoriatic arthritis. Ustekinumab acts by blocking this interleukin activity (5). Ustekinumab exerts its effect in arthritis by blocking this interleukin. Hypersensitivity reactions to biologic agents are categorized into seven types based on clinical phenotype, underlying endotype, and biomarkers: infusion reactions, type I (IgE and non-IgE mediated), cytokine release syndrome, mixed reactions, and type II, III, and IV hypersensitivity reactions (6). Infusion-related and cytokine-release reactions can occur with the first infusion, though the former tends to self-limit with repeated exposure and premedication (7). A study conducted in two tertiary hospitals examined acute infusion reactions to Ustekinumab and suggested they were not immune-mediated, as the reactions occurred on first exposure, resolved with premedication, and most patients tolerated subsequent subcutaneous (SC) injections (8).

This case report presents the successful use of a desensitization protocol in an adult Crohn's Disease patient who experienced a hypersensitivity reaction to Ustekinumab.

Case Report

A 48-year-old female patient had been under follow-up for 13 years due to Rheumatoid Arthritis (RA) and for 2 years due to Crohn's Disease. She was also being monitored for uveitis. The patient had no history of smoking and no known drug allergies. Additionally, she had not been diagnosed with asthma or rhinitis. She was receiving Leflunomide 20 mg for RA. For her Crohn's Disease, the patient had previously been treated with corticosteroids, Methotrexate, and subsequently Infliximab. During the fourth infusion of Infliximab, she experienced mild shortness of breath, and during the fifth infusion, she reported a sensation of throat tightness, shortness of breath, palpitations, and loss of sensation in her legs. These symptoms resolved with treatment, and she was monitored for three hours post-infusion. Following this, her treatment was switched to Ustekinumab by the Gastroenterology department. The initial dose was administered via intravenous infusion, after which she transitioned to subcutaneous (SC) dosing. The fourth SC dose was administered uneventfully. However, during the administration of the fifth SC dose in the emergency room, the patient returned five minutes later with complaints of shortness of breath and palpitations. Her symptoms improved during follow-up. She was referred to our clinic due to her adverse reactions to both infliximab and Ustekinumab. She expressed a desire to continue Ustekinumab treatment due to its therapeutic benefits.

During evaluation, the symptoms were considered adverse drug reactions and scored as 7 on the Naranjo algorithm (9). The patient was desensitized using the subcutaneous protocol adapted from Cohen et al. (10). Written informed consent was obtained from the patient on 19/08/2024. At follow-up, the patient remained asymptomatic. Four additional SC doses, administered every eight weeks, were given using the same protocol with no further adverse reactions, confirming both reproducibility and efficacy.

Discussion

Crohn's Disease is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract, from the mouth to the anus (11). Some patients with Crohn's Disease may experience treatment failure or develop significant side effects. Biological agents, such as Ustekinumab, are generally preferred for patients who do not respond to conventional treatments for chronic diseases. Clinical studies have demonstrated that Ustekinumab possesses a

Table I. Intravenous and Subcutaneous Ustekinumab Desensitization Protocols

#	Solution, mg/mL, formulation	Rate, mL/h for IV formulation	Time, min	Volume, mL administered	Dose administered with this step, mg	Cumulative Dose, mg
1	0.010 IV	2.5	15	0.63	0.00625	0.00625
2	0.010 IV	5	15	1.25	0.01250	0.01875
3	0.010 IV	10	15	2.50	0.02500	0.04375
4	0.010 IV	20	15	5.00	0.05000	0.09375
5	0.104 IV	5	15	1.25	0.13000	0.2275
6	0.104 IV	10	15	2.50	0.26000	0.4875
7	0.104 IV	20	15	5.00	0.52000	1.0075
8	0.104 IV	40	15	10.00	1.04000	2.0475
9	1.032 IV	10	15	2.50	2.5795	4.6270
10	1.032 IV	20	15	5.00	5.1591	9.7861
11	1.032 IV	40	15	10.00	10.3181	20.1042
12	1.032 IV	80	174.375	232.50	239.8958	260.0000
SC Ustekinumab Desensitization (90 mg/mL)						
1	90 SC	N/A	0	0.05	4.5	4.5
2	90 SC	N/A	15	0.1	9	13.5
3	90 SC	N/A	15	0.2	18	31.5
4	90 SC	N/A	15	0.25	22.5	54
5	90 SC	N/A	15	0.4	36	90
IV: intravenous, SC: subcutaneous						

favorable safety profile in the treatment of patients with Crohn's Disease. In the pilot studies UNITI-1 and UNITI-2, the prevalence of adverse events was reported at 65.9% and 55.6%, respectively, which was not significantly different from the placebo groups, which reported 64.9% and 54.3% (12). Furthermore, the incidence of serious adverse events was comparable between patients treated with Ustekinumab and those receiving a placebo. In a case report by Thomas PWA et al., three patients were presented, all of whom experienced immediate reactions to the first dose of IV treatment. Two of these patients attempted to continue treatment via subcutaneous administration, but their medications were ultimately discontinued due to the recurrence of reactions (13). Conversely, in the case report by Cleveland NK et al., no reaction was observed during the first IV infusion in a patient who had previously experienced a reaction. The authors attributed this lack of reaction to the presence of Ethylenediaminetetraacetic Acid (EDTA) in the IV formulation, which was absent in the SC formulation (14).

In the aforementioned cases, reactions were noted during the first IV infusion. However, in our patient, the reaction occurred during the fifth dose and following SC administration. Therefore, we did not classify this as a typical infusion reaction; rather, we considered it to be an IgE-mediated reaction or a mixed reaction.

Although we initially planned to conduct a skin test due to the high cost of the medication, we opted for direct desensitization to ensure that the patient would not have to forgo treatment for an additional two months, particularly given that her physician indicated she was benefiting from the drug.

Drug desensitization is indicated when there are no viable alternatives to the medication or when alternatives are less effective. It involves the administration of gradually increasing doses of the drug under controlled conditions to induce temporary tolerance (15,16).

Given the absence of a standardized desensitization protocol for Ustekinumab, we initially adopted the successful desensitization regimen employed by Cohen et al. in a 9-year-old Crohn's Disease patient, as described in the literature (10). In that case, a 12-step desensitization was performed via IV infusion, followed by subcutaneous administration in subsequent doses, which proved effective and well tolerated.

In conclusion, we report a successful subcutaneous desensitization procedure in an adult Crohn's Disease patient who experienced an adverse reaction to

Ustekinumab. This case underscores the importance of desensitization protocols in enabling the continued use of essential biologics when no alternatives are available. Implementing such protocols can improve patient safety, broaden therapeutic options, and reduce treatment discontinuation due to hypersensitivity.

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